201-16026

Revised

HPV ROBUST SUMMARIES

FOR

DIMETHYL METHYLPHOSPHONATE

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Submitted By:

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1. Substance Information

CAS Number:	756-79-6
Chemical Name:	Dimethyl methylphosphonate
Structural Formula:	$C_3H_9O_3P$
Physical State:	Liquid
Purity:	98.0-99.8%
Synonyms:	DMMP Dimethyl methanephosphonate, Phosphonic acid, methyl dimethyl ester Methanephosphonic acid, dimethyl ester
Uses:	Flame retardant, hydraulic fluid, antifoam agent, plasticizer, textile conditioner, antistatic agent
Exposure Limits:	None

2. Physical – Chemical Properties

2.1 Melting Point:

Method:	Estimation by MPBPWIN program, v1, U.S. EPA/Syracuse Research
Value:	-48°C
Reliability:	2

2.2 Boiling Point:

Identity:	Fyrol DMMP
Method:	OPPTS 730.7220
Year:	Not known
GLP:	No
Value:	180.0°C
Conclusion:	The boiling point of Fyrol DMMP is 180.0°C.
Reliability:	4
Reference:	1

2.3 Vapor Pressure:

Identity:	Fyrol DMMP
Method:	OPPTS 730:7950
Year:	2000
GLP:	No
Value:	0.34 mmHg @ 25°C
Conclusion:	The vapor pressure of Fyrol DMMP is 0.34 mmHg @ 25°C.
Reliability:	2
Reference:	2

2.4 Specific Gravity

Identity:	Fyrol DMMP
Method:	OPPTS 830.7300
Year:	Not known
GLP:	No
Value:	1.16 @ 25°C
Conclusion:	The specific gravity (relative density) of Fyrol DMMP is 1.16 @ 25°C.
Reliability:	4
Reference:	1

2.5 Water Solubility

Identity:	Fyrol DMMP Lot No. 0114E-1
Method:	OECD 105
Year:	2001
GLP:	No
Value:	Fully miscible with water
Conclusion:	DMMP was fully miscible with water, when tested by adding up to 98.4% DMMP to water.
Reliability:	2
Reference:	3

2.6 Octanol:water Partition Coefficient

Identity:	Dimethyl Methylphosphonate
Method:	OPPTS 830.7570
Year:	1988
GLP:	No
Value:	-0.61
Conclusion:	The n-octanol:water partition coefficient (log Kow) was determined by high performance liquid chromatography to be -0.61.
Reliability:	2
Reference:	4

Identity:	Fyrol DMMP Lot No. 0114E-1
Method:	OECD 107
Year:	2001
GLP:	No
Value:	-1.3
Conclusion:	The n-octanol:water partition coefficient (log Kow) was determined by high performance liquid chromatography to be -1.3.
Reliability:	2
Reference:	3

3. Environmental Fate

3.1 Photodegradation

Method:	Estimation by AOP program, v 1.91, U.S. EPA/Syracuse Research
Results:	Half-life = 1.9 d (12-h per day, 1.5 E+06 OH/cm3)
Reliability:	2

3.2 Stability in Water (Hydrolysis)

Identity:	Fyrol DMMP, Batch 03114H0108. Purity: 99.2%
Guideline:	OPPTS 835.2110 and OECD 111 Hydrolysis as a Function of pH
Year:	2004
GLP:	Yes
Method:	In the preliminary study, the hydrolysis of Fyrol DMMP was evaluated in aqueous buffers at pH 4, 7, and 9, over 5 days, at 50°C, at a concentration of 1000 mg/l. The aqueous buffers used at pH 4, 7, and 9 were sodium acetate/acetic acid, potassium dihydrogen phosphate/sodium hydroxide, and potassium chloride/boric acid/sodium hydroxide, respectively. In the definitive test, the hydrolytic stability of Fyrol DMMP was evaluated at pH 9, at 31°, 40°, and 50°C over 30 days. The amount of Fyrol DMMP was determined by extraction of duplicate samples with dichloromethane followed by analysis using gas chromatography with a flame-photometric detector. Calibration standards were prepared and used each time Fyrol DMMP levels were determined. The half-life at 25°C was calculated by extrapolation from the degradation rat constants obtained at the three elevated temperatures.
Results:	In the preliminary test, hydrolytic degradation of Fyrol DMMP was less than 10% at pH 4 and 7, at 50°C. Therefore the half-life of Fyrol DMMP at pH 4 and 7 was estimated to be greater than one year. In the definitive test conducted only at pH 9, the half-lives were calculated as 129 days at 31°C, 46.3 days at 40°C, and 11.8 days at 50°C. Linear regression analysis of the rate constants at each temperature showed the half-life at pH 9 and 25°C to be 307 days.

Reliability: 1
Reference 36

3.3 Biodegradation

Identity: Fyrol DMMP, Batch No. 8114 S-10-1 Purity: 99.6%
Guideline: OECD 301B Ready Biodegradability in the Modified Sturm Test
Year: 1990
GLP: Yes
Method: The chemical oxygen demand (COD) of Fyrol DMMP was determined in triplicate by oxidation with an acid-chromate mixture, using a Fyrol DMMP concentration of 1 g/l. The control standard, potassium hydrogen phthalate, was included in the test. The sealed reaction vials were boiled under reflux at 150°C for two hours. After cooling, the increase in Cr (III) was determined using spectrophotometric methods.
Solutions of 20 mg/l of Fyrol DMMP were used to determine total organic carbon (TOC) and dissolved organic carbon (DOC). TOC was determined with a Photochem organic carbon analyzer. DOC was measured be determining the carbon content of a sample passed through a 0.2 um membrane. In the Modified Sturm Test, the test substance was evaluated in the presence of activated sludge at either 10 mg/l or 20 mg/l. A control vessel contained sodium benzoate at 1 g/l in place of Fyrol DMMP. The vessels were maintained for 27 days during which specified sampling took place. On day 27, the pH was measured in vessel after which HCl was added to remove any carbon dioxide present. The vessels were aerated overnight and DOC was measured on day 28. The theoretical oxygen demand (ThOD), COD, BOD, TCO2, and DOC removal were calculated.
Results: The TCO_2 production for the reference mixture was 128.4 $mgCO_2$ whereas with Fyrol DMMP it was 31.8 $mgCO_2$ at 10 mg/l and 63.6 $mgCO_2$ at 20 mg/l. The mean COD of Fyrol DMMP was 78% of its ThOD. The TOC and DOC levels in distilled water were 105% and 107% of the theoretical organic carbon content, indicating that the test substance was completely oxidized. The blank corrected determinations of DOC of test and reference substances in mgC/l are shown below:

Test Material	Day 0 DOC	Day 28 DOC	% Degradation
Sodium benzoate	11.3	0.2	98
Fyrol DMMP (10 mg)	3.0	2.6	13
Fyrol DMMP (20 mg)	6.2	5.5	11

These results indicate Fyrol DMMP did not readily degrade in this test.
Reliability: 1
Reference: 37

3.4 Fugacity – Transport between Environmental Compartments

Method: Calculation with EPIWIN program, v3.12, US-EPA/Syracuse Research.
Results: Shown below

INPUTS:
Molecular Wt: 124.08
Water solubility: 1E+006 mg/L (calc by model)
Vapor Press: 0.35 mm Hg (user-entered)
Henry's LC: 5.71E-008 atm-m3/mole (calc from Vapor pressure and water solubility)
Log Kow: -0.61 (user-entered)
Soil Koc: 0.101 (calc by model)
Half-Lives based upon Biowin (Ultimate) and Aopwin

EMISSION IN AIR, WATER AND SOIL:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.02	45	1000
Water	41	360	1000
Soil	57.9	720	1000
Sediment	0.0752	3.24e+003	0

EMISSION IN AIR:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	3.3	45	1000
Water	25.5	360	0
Soil	71.2	720	0
Sediment	0.0467	3.24e+003	0

EMISSION IN WATER:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.000848	45	0
Water	99.8	360	1000
Soil	0.0183	720	0
Sediment	0.183	3.24e+003	0

EMISSION IN SOIL:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0984	45	0
Water	22.1	360	0
Soil	77.7	720	1000
Sediment	0.0406	3.24e+003	0

Reliability: 2

4. Ecotoxicity

4.1 Acute Toxicity to Fish

Identity: Fyrol DMMP, Batch No. 8114 S-10-1 Purity 99.4%

Guideline:	OECD 203 Acute Toxicity to Fish
Year:	1990
GLP:	Yes
Method:	Groups of rainbow trout were exposed under static conditions to one of five nominal concentrations (560, 1000, 1800, 3200, and 5600 mg/l) of Fyrol DMMP. Ten fish per group were exposed for 96 hours. A control group was included in the study. Water conditions were: hardness 202-216 mg/l as $CaCO_3$, pH 7.6-8.1, and temperature 13.2-14.9°C. Fish were observed at 0.25, 2, and 24 hours after start of exposure, and thereafter every 24 hours.
Results:	Mortality of 100% was observed in the 3200 and 5600 mg/l groups, while there was no mortality in the 1000 mg/l group. The 96 hour median lethal concentration (LC50) was determined to be 2259 mg/l.
Reliability:	1
Reference:	6

4.2 Toxicity to Microorganisms

Identity:	Fyrol DMMP, Batch No. 8114 S-10-1 Purity 99.4%
Guideline:	OECD 209 Activated Sludge – Respiration Inhibition Test
Year:	1990
GLP:	Yes
Method:	Fyrol DMMP was added to activated sludge containing synthetic sewage, at concentrations of 0, 1, 10, 100, 1000, and 10,000 mg/l, and incubated for 3 hours. 3,5-Dichlorophenol was used as the reference inhibitor.
Results:	The 3,5-dichlorophenol EC50 was 13.6 mg/l, confirming the test was valid. The respiration rate of the control culture did not change during the test. Fyrol DMMP at 1 and 10 g/l inhibited respiration by 20 and 31%, respectively, indicating the product does not substantially inhibit the respiration of activated sludge. The EC50 could not be calculated, but must be greater than 10 g/l.
Reliability:	1
Reference:	5

5 Mammalian Toxicity

5.1 Acute Toxicity

5.11 Acute Oral Toxicity

Identity:	Fyrol DMMP Lot No. 756-79-6 Purity: 99.4%
Guideline:	40 CFR 798.1175 Acute Oral Toxicity
Year:	1982
GLP:	Yes
Method:	Male and female Sprague-Dawley rats received a single 5000 mg/kg oral gavage dose of Fyrol DMMP, and were subsequently observed for signs of

toxicity and for mortality. The animals were observed a minimum of once daily for the 14 day observation period. Necropsies were performed on all animals.

Results: There were minimal signs of toxicity. All animals appeared normal within 24 hours of test substance administration. There were no abnormal findings at necropsy. The acute oral LD50 is > 5 g/kg.

Reliability: 1

Reference: 7

Identity: Dimethyl Methylphosphonate, Sample No. 540811 Purity not stated

Guideline: Federal Hazardous Substances Act Regulations Part 1500

Year: 1981

GLP: Yes

Method: Male and female Sprague-Dawley rats received a single 5000 mg/kg oral gavage dose of dimethyl methylphosphonate and were subsequently observed for signs of toxicity and for mortality. The animals were observed once daily for the 14 day observation period. All animals were weighed on study days 0, 7, and 14. Only animals dying during the study were necropsied.

Results: Signs of toxicity included lacrimation, nasal discharge, and respiratory distress which dissipated within 24 hours. All animals appeared normal by 48 hours. All animals gained body weight during the study. All animals survived the observation period so no necropsies were performed. The acute oral LD50 is > 5 g/kg.

Reliability: 1

Reference: 8

5.12 Acute Dermal Toxicity

Identity: Fyrol DMMP Lot No. 756-79-6 Purity not stated

Guideline: U.S. EPA Guidelines for Registering Pesticides, Fed. Reg. 43:163, 37336

Year: 1982

GLP: Yes

Method: Four male and four female albino rabbits received a dermal application of 2000 mg/kg Fyrol DMMP to their abdominal skin, which was then wrapped for 24 hours. The skin at the application site was abraded on half the animals. After 24 hours, the binding was removed. The animals were observed for 14 days after which they underwent necropsy.

Results: There was no mortality in this study. All rabbits appeared normal thoughout the study, with no clinical signs of toxicity. At necropsy one rabbit showed pale lungs but the other nine animals appeared normal. The acute dermal LD50 is > 2000 mg/kg.

Reliability: 1

Reference: 7

Identity: MCTR-196-77 Lot No. 0717601 Purity not stated

Guideline:	Not stated
Year:	1977
GLP:	No
Method:	Twelve male albino rabbits received a single dermal application of 5000 mg/kg of MCTR-196-77. The skin at the application site was abraded on half the animals. The animals were observed for mortality daily for 14 days.
Results:	There was no mortality in this study. No clinical signs of toxicity were reported. Mild edema and erythema was seen at the application sites on study days one and two. The acute dermal LD50 is > 5000 mg/kg.
Reliability:	2
Reference:	9

Identity:	MCTR-129-78 Lot No. VGC-89549 Purity: 98.6%
Guideline:	Not stated
Year:	1978
GLP:	No
Method:	Twelve male albino rabbits received a single dermal application of 5000 mg/kg of MCTR-129-78. The skin at the application site was abraded on half the animals. The animals were observed for mortality daily for 14 days.
Results:	There was no mortality in this study. No clinical signs of toxicity were reported. Mild edema and erythema were observed at the application sites for up to 48 hours. The acute dermal LD50 is > 5000 mg/kg.
Reliability:	2
Reference:	10

Identity:	Dimethyl Methylphosphonate, Sample N. 540811 Purity not stated
Guideline:	Federal Hazardous Substances Act Regulations Part 1500
Year:	1981
GLP:	Yes
Method:	Six albino rabbits received dermal application of 2000 mg/kg dimethyl methylphosphonate to approximately 10% of the body surface. Three of the six application sites were abraded. The application sites were then wrapped for 24 hours. The animals were observed for mortality for 14 days.
Results:	There was no mortality in this study. There were no signs of irritation at the application sites. The acute dermal LD50 is > 2000 mg/kg.
Reliability:	1
Reference:	11

5.13 Acute Eye Irritation

Identity:	Fyrol DMMP Lot No. 756-79-6 Purity not stated
Guideline:	U.S. EPA Guidelines for Registering Pesticides, Fed. Reg. 43:163, 37336
Year:	1982
GLP:	Yes
Method:	Nine albino rabbits received 0.1 ml of Fyrol DMMP in one eye of each rabbit. The other eye acted as a corresponding control. Six of the treated eyes remained unwashed for the duration of the study, while three of the treated eyes were rinsed with water. The animals were observed daily for seven days. The study was terminated on the seventh day because there was no eye irritation. The treated eyes were examined 24, 48, and 72 hours after treatment, and on days 4 and 7. The eye irritation was scored according to Draize
Results:	Fyrol DMMP caused mild conjunctival irritation in six unwashed eyes and in one washed eye. This irritation cleared by day 4. The average draize for conjunctival irritation score at 24 and 72 hours, and at 4 days are 3.3, 0.7, and 0.0, respectively. Fyrol DMMP is a mild eye irritant.
Reliability:	1
Reference:	7

Identity:	MCTR-129-78 Lot No. VGC-89549 Purity: 98.6%
Guideline:	Federal Hazardous Substance Labeling Act Section 1500.42
Year:	1978
GLP:	No
Method:	Six albino rabbits each received 0.1 ml of the test material in one eye. The other eye served as the nontreated control eye. The treated eyes remained unwashed during the 7 day observation period. Ocular reaction to the test substance was graded according to Draize.
Results:	MCTR-129-78 caused mild irritation to the conjunctivae, but caused no irritation to the cornea or iris. The test substance is a mild eye irritant.
Reliability:	2
Reference:	12

Identity:	Dimethyl Methylphosphonate Sample No. 540811 Purity not stated
Guideline:	Federal Hazardous Substance Labeling Act Section 1500.42
Year:	1981
GLP:	Yes
Method:	Six albino rabbits each received 0.1 ml of the test material in one eye. The other eye served as the nontreated control eye. The treated eyes remained unwashed during the 72 hour observation period. Ocular reaction to the test substance was graded according to Draize.
Results:	There was no irritation to the cornea or iris. Mild irritation to the conjunctiva and minimal chemosis was observed through 24 hours. No irritation was observed beyond 24 hours. DMMP was a very mild eye irritant in this study.
Reliability:	1

Reference: 13

5.14 Skin Irritation

Identity: Fyrol DMMP Lot No. 756-79-6 Purity not stated
Guideline: U.S. EPA Guidelines for Registering Pesticides, Fed. Reg. 43:163, 37336
Year: 1982
GLP: Yes
Method: Six albino rabbits received 0.5 ml of Fyrol DMMP applied to a previously shaven area of their skin. The skin at the application sites of the rabbits was abraded prior to the administration of the test substance. The sites were covered for 24 hours, after which they were uncovered and examined for irritation. The sites were scored for irritation according to Draize. The study was terminated after the 72 hour examination of the application sites.
Results: There was no irritation at any of the application sites. Fyrol DMMP was determined to be nonirritating to the skin in this test.
Reliability: 1
Reference: 7

Identity: MCTR-129-78 Lot No. VGC-89549 Purity: 98.6%
Guideline: Federal Hazardous Substance Labeling Act Section 1500.41
Year: 1978
GLP: No
Method: Six albino rabbits received 0.5 ml of MCTR-129-78 applied to skin sites where the fur had been previously clipped. Each animal had both abraded and nonabraded application sites. After application, the sites were covered for 24 hours. After removal of the covering, the sites were examined for irritation through 72 hours after treatment. The treatment sites were scored for irritation according to the method of Draize.
Results: Mild irritation was observed at 24 hours by not at 72 hours. The authors concluded that MCTR-129-78 was not a dermal irritant.
Reliability: 2
Reference: 14

Identity: Dimethyl Methylphosphonate, Sample No. 540811 Purity not stated
Guideline: Federal Hazardous Substances Act Regulations Part 1500
Year: 1981
GLP: Yes
Method: Six albino rabbits received a dermal application of 0.5 mg of dimethyl methylphosphonate to one abraded and one nonabraded skin site. The application sites were then covered for 24 hours. When unwrapped, the sites were examined at 24 and 72 hours for irritation. If irritation was present, it was scored according to Draize.

Results: Very slight irritation was observed at 24 and 72 hours. Thus the test substance was identified as a slight irritant.
Reliability: 1
Reference: 15

5.15 Acute Inhalation

Identity: Dimethyl Methylphosphonate Lot No. and Purity not stated
Guideline: Not stated
Year: 1974
GLP: No
Method: Five male and five female Sprague-Dawley rats were exposed to a nominal concentration of 26.1 mg/l for one hour, in a positive pressure inhalation chamber. The animals were then observed for 14 days for signs of toxicity and for mortality. No necropsy was performed.
Results: Aside from moderate depression which disappeared within hours of removal from the chamber, the animals did not exhibit clinical signs of toxicity. There was no mortality in this study. The inhalation LC50 in this study is greater than nominal 26.1 mg/l.
Reliability: 3
Reference: 16

Identity: MCTR-196-77 Lot No. 0717601 Purity not stated
Guideline: Not stated.
Year: 1977
GLP: No
Method: Ten laboratory rats were exposed to a single nominal concentration of 20.27 mg/l for one hour. The animals were observed for clinical signs of toxicity and for mortality. The duration of the observation period is not stated. Necropsies were not performed.
Results: Minimal signs of toxicity were observed. There was no mortality in this study. The inhalation LC50 is greater than nominal 20.27 mg/l.
Reliability: 3
Reference: 17

Identity: MCTR-129-78 Lot No. VGC-89549 Purity: 98.6%
Guideline: U.S. EPA Guideline for Pesticide Hazard Evaluation, Subpart F
Year: 1978
GLP: Yes
Method: Five male and 5 female Sprague-Dawley rats were exposed to a single nominal concentration of 20.13 mg/l for one hour. The animals were observed for clinical signs of toxicity and for mortality for 14 days post-exposure. Body weights were taken on days 0, 7, and 14. Necropsies were performed on all animals.
Results: Various signs of toxicity were observed, including ataxia, stained face and fur, and piloerection. One female rat died approximately 24 hours after

exposure. At necropsy one animal was found to have hemorrhagic lungs while the remaining nine animals showed no gross anomalies. Some animals showed a slight loss in body weight. The acute inhalation LC50 in this study is greater than nominal 20.13 mg/l.

Reliability: 3
Reference: 18

5.2 Repeated Dose Toxicity

Identity: Dimethyl Methylphosphonate Lot No. 4182-2 Purity not stated in report.
Guideline: Not stated National Toxicology Test
Year: 1981
GLP: Yes
Method: Ten male and ten female Fischer 344 rats received either 0, 250, 500, 1000, 2000, or 4000 mg/kg daily via oral gavage, five days per week, for thirteen weeks. The animals were housed five per cage. The animals were observed for clinical signs and mortality during the in-life phase. Weekly body weights were recorded. All animals were necropsied, at which time tissues and organs were removed from each animal for diagnostic pathology. Apparently no clinical chemistry measurements were made in this study.
Results: All of the rats in the 4000 mg/kg/day group died during the first week of treatment. In the 2000 mg/kg/day group, 6/10 males and 3/10 females died during the study, suggesting that this dose is significantly above the Maximum Tolerated Dose (MTD). There was only one mortality in the 1000 mg/kg/day group. Minimal clinical signs were reported. These included lacrimation and eye crust, which were observed in almost all animals, including non-treated control rats. No treated-related clinical signs were reported. Animals in all but the highest dose group showed body weight gains throughout the study. Necropsy revealed no gross lesions attributable to treatment. Liver weights were elevated in the male and female rats that received 2000 mg/kg/day. Microscopic examination of the tissues revealed minimal to mild non-treatment related effects in the kidneys, testes, and salivary glands. Although the animals may have had a low grade SDA virus which possibly accounted for the salivary gland changes, SDA infections do not impart target organ toxicity in rats and thus the infection did not significantly impact the conduct of this study or the validity of the results. LOAEL (M): 250 mg/kg/day, NOAEL (F): 1000 mg/kg/day
Reliability: 2
Reference: 19

Identity: Dimethyl Methylphosphonate Lot No. EA113077 Purity > 98%
Guideline: Not stated National Toxicology Test
Year: 1981
GLP: Yes
Method: Ten male and ten female B6C3F1 mice received either 0, 250, 500,

1000, 2000, 4000, or 8000 mg/kg daily via oral gavage, five days per week, for thirteen weeks. The animals were housed five per cage. The animals were observed for clinical signs and mortality during the in-life phase. All animals were necropsied, at which time tissues and organs were removed from each animal for diagnostic pathology. No clinical chemistry measurements were made in this study.

Results: All of the mice in the 8000 mg/kg/day group and 9/10 each of the males and females of the 4000 mg/kg/day group died during the study, indicating this dose is significantly above the Maximum Tolerated Dose. No compound-related clinical signs or gross or microscopic lesions were observed. There were no morphologic effects on the reproductive organs. The NOAEL is 2000 mg/kg/day.

Reliability: 2

Reference: 19

Identity: Dimethyl methylphosphonate Lot Nos.: 4182-2 (~98%), L120381 (purity not stated), 1114L-6-1 (>99%), 114L-2-1 (~99%)

Guideline: National Toxicology Program Carcinogenicity Bioassay

Year: 1987

GLP: Yes

Method: Groups of 50 male and 50 female Fischer 344 rats received either 0, 500, or 1000 mg/kg dimethyl methylphosphonate (DMMP) in corn oil via gavage, five days per week for 103 weeks. The animals were housed five per cage. All animals were observed twice daily. Animals found moribund were humanely terminated and examined via necropsy. At the conclusion of the study, all animals were examined during necropsy and specified tissues were removed, weighed, and placed in formalin for diagnostic pathology. All specified tissues were subsequently evaluated by microscopic examination.

Results: Survival of male rats in all groups was greater than 50% until week 80, after which survival decreased to 27/50 in the control group, 17/50 in the low dose group, and 4/50 in the high dose males. This decreased survival in dosed male rats was considered to be due in part to DMMP-related kidney toxicity. Survival of the high dose female rats also decreased, but not as substantially as in the males. Near the end of the in-life phase, the body weights of the high dose male and female rats were significantly lower than the body weights of the corresponding control animals. No DMMP-related clinical signs were reported in the treated rats.

In male rats, DMMP treatment resulted in nephropathy of the collecting tubules of the kidneys (12/50 controls, 41/50 low dose, 36/49 high dose) and focal hyperplasia in the renal tubules (0/50, 8/50, 9/49. Incidence of testicular atrophy was not significant (0/50, 2/50, 2/49). There was no evidence of reduced spermatogenesis or other effects on the reproductive system.

No non-neoplastic treatment-related effects were reported in other organs. Neoplastic effects in male rats (renal tubular cell adenocarcinoma) are discussed under carcinogenicity. No NOAEL for non-neoplastic effects

was established for male rats. In female rats, there were no renal tubule alterations. No treatment-related effects were reported in any other organs, either macroscopically or microscopically, including the reproductive organs. NOAEL for non-neoplastic effects in female rats: 500 mg/kg/day.

Reliability: 1
Reference: 31

Identity: Dimethyl methylphosphonate Lot Nos.: 4182-2 (~98%), L120381 (purity not stated), 1114L-6-1 (>99%), 114L-2-1 (~99%)
Guideline: National Toxicology Program Carcinogenicity Bioassay
Year: 1987
GLP: Yes
Method: Groups of 50 male and 50 female B6C3F1 mice received either 0, 1000, or

2000 mg/kg dimethyl methylphosphonate (DMMP) in corn oil via gavage, five days per week for 102 weeks. The animals were housed five per cage. All animals were observed twice daily. Animals found moribund were humanely terminated and examined via necropsy. At the conclusion of the study, all animals were examined during necropsy and specified tissues were removed, weighed, and placed in formalin for diagnostic pathology. All specified tissues were subsequently evaluated by microscopic examination.

Results: The body weights of the high dose male mice were significantly lower than those of the corresponding control animals between weeks 36 and 76. A similar reduction was seen in the few surviving high dose female mice from week 88. No DMMP-related clinical signs were reported in the treated mice. Mortality was high during the study, particularly in high dose animals. Deaths in high dose male mice between weeks 23 and 45 were associated with fighting. Deaths of 17 high dose males and 22 high dose females during week 45 were associated with administration of a concentration of test material 34% more than the targeted amount, due to improper resuspension of the dose mixture. Eleven low dose males died on the same day during week 77. Although the cause of death was not established, it may also have been due to improper handling of the dose mixtures. Lung congestion was seen in the mice that died at weeks 45 and 77, but not in mice surviving to the end of the study. Survival at the end of the study in male mice was 29/50 in vehicle control, 12/50 in the low dose and 0/50 in the high dose, and in female mice, 41/50, 30/50, and 2/50, respectively. No clearly treatment-related cause of death was reported.

No treatment-related effects were noted, either macroscopically or microscopically, in the reproductive organs of either male or female mice. No effects were reported in other organs. No NOAEL was established for non-neoplastic effects due to the high mortality in the study.

Reliability: 1
Reference: 31

5.3 Genetic Toxicity

5.3.1 In Vitro Gene Mutation

Identity:	Dimethyl methylphosphonate Lot No. and purity not stated
Guideline:	Bacterial Reverse Mutation Test (Ames Test)
Year:	1983
GLP:	Not known
Method:	DMMP was added as a solution in water to *Salmonella typhimurium* tester strains TA-1535, TA-1537, TA-98, and TA-100 at doses ranging from 100 to 10,000 ug/plate. Toxicity was seen at the top dose level. The test was conducted in the presence and absence of an Aroclor 1254 induced rat or hamster liver metabolic activating system. Revertants were presented from 3 plates per dose level. Positive control chemicals (2-aminoantracene, 4-nitro-o-phenylenediamine, sodium azide, and 9-aminoacridine) were used to confirm the validity of the test.
Results:	DMMP showed no mutagenic activity in any strain, with our without metabolic activation. The positive control showed mutagenic activity thus confirming the validity of the test.
Reliability:	2
Reference:	31

Identity:	Fyrol DMMP Lot No. 9114H-17 Purity not stated.
Guideline:	Bacterial Reverse Mutation Test (Ames Test)
Year:	1981
GLP:	Yes
Method:	Fyrol DMMP was added to five *Salmonella typhimurium* tester strains (TA-1535, TA-1537, TA-1538, TA-98, TA-100) at doses ranging from 0.62 to 50 ul/plate. The test was conducted in the absence and presence of an Aroclor 1254 or Phenobarbital induced rat and mouse liver metabolic activating system. Positive control chemicals (sodium azide, 9-amino acridine, 2-nitrofluorene and 2-aminoanthracene) was used to confirm the validity of the test.
Results:	Significant toxicity was seen at the high dose, 50 ul/plate. Fyrol DMMP did not express mutagenic activity in the Ames *Salmonella* assay in the presence or absence of a metabolic activating system.
Reliability:	1
Reference:	20

Identity:	MCTR-196-77, Lot No. 0717601 Purity not stated
Guideline:	Bacterial Reverse Mutation Test (Ames Test)
Year:	1977
GLP:	No
Method:	MCTR-196-77 was added to five *Salmonella typhimurium* tester strains (TA-1535, TA-1537, TA-1538, TA-98, TA-100) at doses ranging from 0.001 to 5 ul/plate. The test was conducted in the absence and presence of an Aroclor 1254 induced rat liver metabolic activating system. Positive

control chemicals were used to confirm the validity of the test.

Results: MCTR-196-77 was mutagenic in two *Salmonella* strains, TA-1538 and TA-98, in the presence of a metabolic activating system.
[These positive results were superceded in Ref. 18 as result of lab review. Due to a technician error, MCTR-196-77 was retested.]

Reliability: 2

Reference: 21

Identity: MCTR-196-77, Lot No. 0717601 Purity not stated

Guideline: Bacterial Reverse Mutation Test (Ames Test)

Year: 1978

GLP: No

Method: The testing facility concluded that the results cited in Ref. 17 were in error probably due to an incorrect addition of chemical to the test by a technician. The data, when carefully reviewed, indicated that the positive control chemical was probably added to the plates of TA-1538 and TA-98 rather than the test compound. MCTR-196-77 was retested with *Salmonella* strain TA98 at doses ranging from 0.001 to 5 ul/plate. The test was conducted in the presence of an Aroclor 1254 induced rat liver metabolic activating system. Only TA98 was retested as it is more sensitive than TA-1538.

Results: As TA-98 did not demonstrate mutagenic activity, it was concluded that MCTR-196-77 did not demonstrate mutagenic activity in any of the assays in the evaluation in the presence or absence of a metabolic activating system. This conclusion supersedes the earlier conclusion in the August 1977 report (Ref. 17).

Reliability: 2

Reference: 22

Identity: MCTR-196-77, Lot. No. 0717601 Purity not stated

Guideline: Bacterial Reverse Mutation Test (Ames Test)

Year: 1977

GLP: No

Method: MCTR-196-77 was added to five *Salmonella typhimurium* tester strains (TA-1535, TA-1537, TA-1538, TA-98, TA-100) at five doses, which differed per tester strain. The test was conducted in the absence and presence of an Aroclor 1254 induced rat liver metabolic activating system. Positive control chemicals were used to confirm the validity of the test.

Results: MCTR-196-77 did not demonstrate mutagenic activity in any of the five tester strains in the presence or absence of a metabolic activating system.

Reliability: 2

Reference: 23

Identity: MCTR-129-78 Lot No. VGC 89549 Purity: 98.6%

Guideline: Bacterial Reverse Mutation Test (Ames Test)

Year: 1978

GLP:	No
Method:	MCTR-129-78 was added to five *Salmonella typhimurium* tester strains (TA-1535, TA-1537, TA-1538, TA-98, TA-100) at doses ranging from 0.01 to 10 ul/plate. The test was conducted in the absence and presence of an Aroclor 1254 induced rat liver metabolic activating system. Positive control chemicals were used to confirm the validity of the test.
Results:	MCTR-129-78 did not demonstrate mutagenic activity in any of the five tester strains in the presence or absence of a metabolic activating system.
Reliability:	2
Reference:	24

Identity:	Dimethyl Methylphosphonate Lot No. and purity not stated
Guideline:	In Vitro Mammalian Cell Gene Mutation Test
Year:	1983
GLP:	Not known
Method:	Dimethyl methylphosphonate was evaluated in the L5178Y mouse lymphoma cell assay at doses ranging from 0.25 to 5.0 ul/ml in the absence of a metabolic activating system, with distilled water used as solvent. A positive control chemical (methyl methanesulfonate) was included in the test to confirm validity.
Results:	Dimethyl methylphosphonate showed a dose-related increase in mutation frequency at all dose levels, which was significant at the two highest doses (3.0 and 5.0 ul/ml). The test substance is therefore considered a mutagen in this test system without metabolic activation. The positive control chemical was mutagenic, validating the sensitivity of the assay.
Reliability:	2
Reference:	31

Identity:	Fyrol DMMP Lot No. 9114H-17 Purity 99.5%
Guideline:	In Vitro Mammalian Cell Gene Mutation Test
Year:	1981
GLP:	Yes
Method:	Fyrol DMMP was added to L5178Y mouse lymphoma cell cultures at ten different doses. Positive control chemicals (ethyl methanesulfonate and n-nitrosodimethylamine) were added to other mouse lymphoma cells to confirm the validity of the assay. Fyrol DMMP was tested in the absence and presence of a rat liver metabolic activating system.
Results:	In the absence of an activating system, Fyrol DMMP demonstrated mutagenic activity in a dose-related manner, with significant mutation frequency at 35 ul/ml. In the presence of a rat liver metabolic activating system, Fyrol DMMP expressed mutagenic activity at all dose levels above 5.0 ul/ml. Fyrol DMMP demonstrated mutagenic activity, in the form of gene mutation, in the absence and presence of an activating system, in the L5178Y mouse lymphoma mammalian cell assay.
Reliability:	1
Reference:	25

Identity:	Dimethyl Methylphosphonate, Sample No. 540811 Purity not stated
Guideline:	In Vitro Mammalian Cell Gene Mutation Test
Year:	1981
GLP:	Yes
Method:	Dimethyl methylphosphonate was evaluated in the L5178Y mouse lymphoma cell assay at doses ranging from 7.5 ul/ml to 42.2 ul/ml, with and without an Aroclor-induced rat liver metabolic activating system. Appropriate positive control chemicals (2-amino anthracene, 2-acetylamino fluorene, and benzopyrene) were included in the assay to assure validity.
Results:	Dimethyl methylphosphonate demonstrated a dose-related increase in mutation frequency with increasing doses, in both the activated and nonactivated mammalian cell systems.
Reliability:	1
Reference:	26

5.3.2 In Vitro Chromosome Aberrations

Identity:	Dimethyl methylphosphonate Lot No. and Purity not stated
Guideline:	In Vitro Mammalian Chromosomal Aberration Test
Year:	1983
GLP:	Not known
Method:	Dimethyl methylphosphonate was evaluated for sister chromatid exchanges in the Chinese Hamster Ovary Cells. The cells were incubated with the test substance at doses from 1100 to 11,000 ug/l without metabolic activation and from 1100 to 22,000 ug/ml with rat liver metabolic activation system. Cells were cultured for a sufficient time to second metaphase division. Positive control chemicals were included to confirm the validity of the assay.
Results:	Dimethyl methylphosphonate showed mutagenic activity with and without metabolic activation. The positive controls showed strong positive activity and thus confirmed the validity of the assay.
Reliability:	2
Reference:	31

Identity:	Dimethyl methylphosphonate Lot No. and purity not stated
Guideline:	In Vitro Mammalian Chromosomal Aberration Test
Year:	1983
GLP:	Not known
Method:	Chinese hamster ovary cells were incubated with dimethyl methylphosphonate at doses from 2000 to 22,000 ug/ml with and without an induced rat liver metabolic activating system. Cells were cultured for a sufficient time to reach first metaphase division. Positive control chemicals were included in the test to confirm validity.
Results:	Dimethyl methylphosphonate did not demonstrate mutagenicity activity with or without metabolic activation. The positive controls showed strong positive effects and thus confirmed he validity of the assay.

Reliability: 2
Reference: 31

Identity: Fyrol DMMP Lot No. 9114H-17 Purity 99.5%
Guideline: In Vitro Mammalian Chromosomal Aberration Test
Year: 1982
GLP: Yes
Method: Fyrol DMMP was added to L5178 mouse lymphoma cells at doses ranging from 5.0 ul/ml to 45 ul/ml, in the presence and absence of an Aroclor 1254 rat liver metabolic activating system. Positive control chemicals were added to L5178 cell to confirm the validity of the assay. After exposure to the test substance, the cells were evaluated for chromosomal aberrations and sister chromatid exchanges.
Results: Fyrol DMMP induced a significant increase in various types of chromosomal aberrations and sister chromatid exchanges in the presence and absence of a metabolic activating system. These increases in mutagenic activity occurred in a dose-related manner.
Reliability: 1
Reference: 27

5.3.3 In Vivo Mutagenicity Tests

Identity: Dimethyl methylphosphonate Lot No. and purity not stated
Guideline: Sex-linked Recessive Lethal Test in *Drosophila melanogaster*
Year: 1983
GLP: Not known
Method: Dimethyl methylphosphonate was fed to adult male fruit flies at a dose of 23,735 ppm. Treated and control males were mated with non-treated females. The offspring were examined to determine the incidence of sex-linked recessive mutations.
Results: The offspring of dimethyl methylphosphonate treated males showed a significant increase in lethal mutations.
Reliability: 2
Reference: 31

Identity: Dimethyl methylphosphonate Lot No. and purity not stated
Guideline: Induction of Reciprocal Translocations in *Drosophila melanogaster*
Year: 1983
GLP: Not known
Method: Dimethyl methylphosphonate was fed to adult male fruit flies at a dose of 23,500 ppm. Treated and control flies were mated to non-treated females. The F1 males were then back crossed with bw:st females.
Results: Dimethyl methylphosphonate treatment did not cause a significant increase in translocations. Dimethyl methylphosphonate was not mutagenic in this test.
Reliability: 2

Reference: 31

Identity: Fyrol DMMP Lot No. 1114L-6-1 Purity not stated
Guideline: Sex-linked Recessive Lethal Test in *Drosophila melanogaster*
Year: 1982
GLP: Yes
Method: Fyrol DMMP was fed to adult male fruit flies (*Drosophila melanogaster*) at one of two dose levels. Additional male flies were included in negative and positive control groups. The treated and negative control males were then mated with nontreated females. The offspring were examined to determine the incidence of sex-linked recessive lethal mutations.
Results: Fyrol DMMP did not induce sex-linked recessive lethal mutations, as there was no increase in the frequency of mutations except in the positive control flies. Fyrol DMMP did not demonstrate mutagenic activity in this assay.
Reliability: 1
Reference: 28

Identity: Fyrol DMMP Lot No. 9114H-17 Purity 99.5%
Guideline: Mammalian Bone Marrow Chromosomal Aberration Test
Year: 1982
GLP: Yes
Method: Male Sprague-Dawley rats received either a single dose or five consecutive doses of Fyrol DMMP, at dose levels from 556 to 5000 mg/kg/day. Three hours prior to sacrifice, the animals received an intraperitoneal injection of colchicine to arrest the cells in metaphase. Animals were sacrificed either 6, 12, 24, or 48 hours after dosing. Bone marrow cells were collected from the tibia and/or femur, processed and placed on slides, and the cells were examined for structural changes to the chromosomes, and rearrangements of chromosomes. Positive and negative groups were included in the study.
Results: There was no increase in the frequency of chromosomal aberrations or rearrangements in the treated animals when compared to the negative control group. The positive control, cyclophosphamide, induced a significant increase in chromosomal aberrations. Fyrol DMMP was not mutagenic in this assay.
Reliability: 1
Reference: 29

5.3.4 In Vitro Mammalian Cell Transformation

Identity: Fyrol DMMP Lot No. 9114H-17 Purity 99.5%
Guideline: Not stated.
Year: 1983
GLP: Yes
Method: To determine whether Fyrol DMMP is able to transform cultures of normal BALB/3T3 cells, the cells were exposed to the test material at

doses ranging from 0.625 ul/ml to 10 ul/ml, for about 5 weeks. The flasks were then examined for transformed foci.

Results: A dose-dependent increase in the number of transformed foci was observed. Although this increase did not exceed 1.7 times the control (background transformation) values, it was statistically significant and indicates that Fyrol DMMP has weak mammalian cell transforming activity.

Reliability: 1

Reference: 30

5.4 Carcinogenicity

Identity: Dimethyl methylphosphonate Lot Nos.: 4182-2 (~98%), L120381 (purity not stated), 1114L-6-1 (>99%), 114L-2-1 (~99%)

Guideline: National Toxicology Program Carcinogenicity Bioassay

Year: 1987

GLP: Yes

Method: Groups of 50 male and 50 female Fischer 344 rats received either 0, 500, or 1000 mg/kg dimethyl methylphosphonate (DMMP) in corn oil via gavage, five days per week for 103 weeks. The animals were housed five per cage. All animals were observed twice daily. Animals found moribund were humanely terminated and examined via necropsy. At the conclusion of the study, all animals were examined during necropsy and specified tissues were removed, weighed, and placed in formalin for diagnostic pathology. All specified tissues were subsequently evaluated by microscopic examination.

Results: Non-neoplastic effects of DMMP are described under repeat dose toxicity. DMMP treatment resulted in nephropathy of the collecting tubules of the kidneys in the male rats (12/50 controls, 41/50 low dose, 36/49 high dose), focal hyperplasia in the male rat renal tubules (0/50, 8/50, 9/49), and the occurrence of renal tubular cell adenocarcinoma (0/50, 2/50, 3/49). There were no renal tubule alterations in the female rats. The NTP concluded that there was some evidence of carcinogenic activity in the male rats based on the occurrence of the renal tubule adenocarcinomas. The NTP did not equate the formation of the renal tumors to the presence of hyaline droplets present in the renal tubule epithelial cells, reported by the study pathologist, even though it is well recognized that a male rat specific mechanism has been identified that correlates the presence of the hyaline droplets with the induction of alpha-2u-globulin and the subsequent induction of renal tumors. The lack of renal tumors in the female rats supports the alpha-2u-globulin mechanism which is specific to the male rat. An significantly increased incidence of mononuclear cell leukaemia was reported in high dose male rats (10/50, 11/50, 17/50).
There was no increase in incidence of tumors in female rats. The NTP concluded that there was no evidence of carcinogenic activity in female rats.

Reliability: 1

Reference:	31
Identity:	Dimethyl methylphosphonate Lot Nos.: 4182-2 (~98%), L120381 (purity not stated), 1114L-6-1 (>99%), 114L-2-1 (~99%)
Guideline:	National Toxicology Program Carcinogenicity Bioassay
Year:	1987
GLP:	Yes
Mathod:	Groups of 50 male and 50 female B6C3F1 mice received either 0, 1000, or 2000 mg/kg dimethyl methylphosphonate (DMMP) in corn oil via gavage, five days per week for 103 weeks, five days per week for 102 weeks. The animals were housed five per cage. All animals were observed twice daily. Animals found moribund were humanely terminated and examined via necropsy. At the conclusion of the study, all animals were examined during necropsy and specified tissues were removed, weighed, and placed in formalin for diagnostic pathology. All specified tissues were subsequently evaluated by microscopic examination
Results:	Survival at the end of the study in male mice, was 29/50 in vehicle control, 12/50 in the low dose and 0/50 in the high dose, and in female mice, 41/50, 30/50, and 2/50, respectively. While the NTP reports the mouse segment as "an inadequate study of carcinogenic activity because of decreased survival," it is important to note that even though the high dose was clearly above the Maximum Tolerated Dose, DMMP did not induce a significant incidence of tumors in any tissue in either male or female mice.
Reliability:	1
Reference:	31

5.5 Reproductive Toxicity

Identity:	Fyrol DMMP Lot No. 1114L-6-1 and 1114L-2-1 Purity: >99%
Guideline:	National Toxicology Program Special Study
Year:	1984
GLP:	Yes
Method:	Five groups of 20 male Fischer 344 rats received 0, 250, 500, 1000, or 2000 mg/kg of DMMP, via gavage, five days per week for ninety days. They were then mated with untreated female Fischer 344 rats. Endpoints measured include sperm count and motility, mating index, number of resorptions, LH and FSH levels, and the histopathology of the male reproductive organs.
Results:	There was a dose-related decrease in sperm count, sperm motility, and mating index. The male fertility index was 70, 75, 60, 40, and 0 in the 0, 250, 500, 1000, and 2000 mg/kg groups, respectively. DMMP expressed activity as a dominant lethal mutagen by increasing the number of early resorptions with increasing dose (control 6.1% vs 14.9, 37.8, and 79.1%). Microscopic examination of the testes revealed histologic abnormalities only in the high dose group. These changes included decreased spermatogenesis and degenerative lesions.
Reliability:	1
Reference:	32

Identity:	Fyrol DMMP Lot No. 1114L-6-1 and 1114L-2-1 Purity: >99%
Guideline:	National Toxicology Program Special Study
Year:	1984
GLP:	No
Method:	Male Fischer 344 rats received 1750 mg/kg DMMP via oral gavage daily for up to 12 weeks. Reproductive tissues were collected and processed for examination by light microscopy. A reversibility phase was included in the study.
Results:	Daily oral treatment with DMMP resulted in changes to spermatogenesis and to the seminiferous tubule morphology. A significant alteration of sperm maturation and spermiation was observed, with degenerative lesions in the tubules. After a 14 week recovery period, the treated animals showed significant but incomplete reversal of the DMMP effects. DMMP did not adversely affect the epididymis.
Reliability:	2
Reference:	33

Identity:	Fyrol DMMP Lot No. 1114L-6-1 Purity: >99%
Guideline:	National Toxicology Program Special Study
Year:	1984
GLP:	No
Method:	Groups of male B6C3F1 mice were treated with either 0, 250, 500, 1000, or 2000 mg/kg DMMP by gavage, five days per week for 13 weeks. The treated males were mated with untreated female mice.
Results:	The two highest doses resulted in an increase in early resorptions, which suggests a dominant lethal effect. After a 15 week recovery period, there were no remaining adverse effects. Male mice are less responsive than the male rat to the reproductive toxicity of DMMP.
Reliability:	2
Reference:	34

5.6 *Developmental Toxicity (Teratogenicity)*

Identity:	Dimethyl Methylphosphonate Lot No. and purity not stated
Guideline:	EPA Subdivision F Section 83-3
Year:	1978
GLP:	No
Method:	Groups consisting of 25 pregnant Sprague-Dawley rats each received either CMC (vehicle) or DMMP at 100, 1000, or 2000 mg/kg/day via oral gavage from gestation day 6 through day 15. The pregnant animals were sacrificed on gestation day 21 and the fetuses were removed, weighed, sexed, and examined microscopically for malformations (developmental anomalies).
Results:	The high dose, 2000 mg/kg/day, caused maternal toxicity which was expressed as decreased body weight gain and decreased food

consumption. Although an examination of the fetuses from this group showed fetotoxicity, seen as lower body weights and delayed skeletal development, there was no increase in the incidence of fetal malformations. Dimethyl methylphosphonate did not demonstrate teratogenic activity in this study.

Reliability: 2
Reference: 35

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